Blood Pressure Regulation

Introduction

This lesson is about blood pressure homeostasis—the mechanisms that detect changes in blood pressure and the responses to correct it. Too much blood pressure will blow out a tissue; too little pressure and the tissue is starved of necessary nutrients. We are talking about both **systemic blood pressure regulation**—throughout the body as a whole—and **regional blood pressure regulation**—in the tissues perfused by a given arteriole. Remember that the systemic blood pressure is controlled by the arterioles, the only vessels that can meaningfully alter the size of their lumen through vasodilation and vasoconstriction. At the regional level, one arteriole listens to the tissue it provides blood flow to and keeps the flow where the tissue wants it (by controlling the resistance, delivering only the volume of flow to produce the pressure those tissues want). And on the microscopic level, we find mechanisms with which we close this lesson.

The majority of the lesson, however, is on systemic blood pressure regulation at the macroscopic level. The body has sensors for changes in blood pressure—baroreceptors in central arteries and the nephrons of the kidney—and effectors that can change blood pressure. Logically (and mathematically), the mean arterial blood pressure is supported by the cumulative vasoconstriction or vasodilation of all arterioles (systemic vascular resistance), how many times the heart beats per minute (heart rate), how hard the hard beats (contractility), and how much blood there is to eject into the aorta (preload). And with that, we have the introduction of the MAP equation.

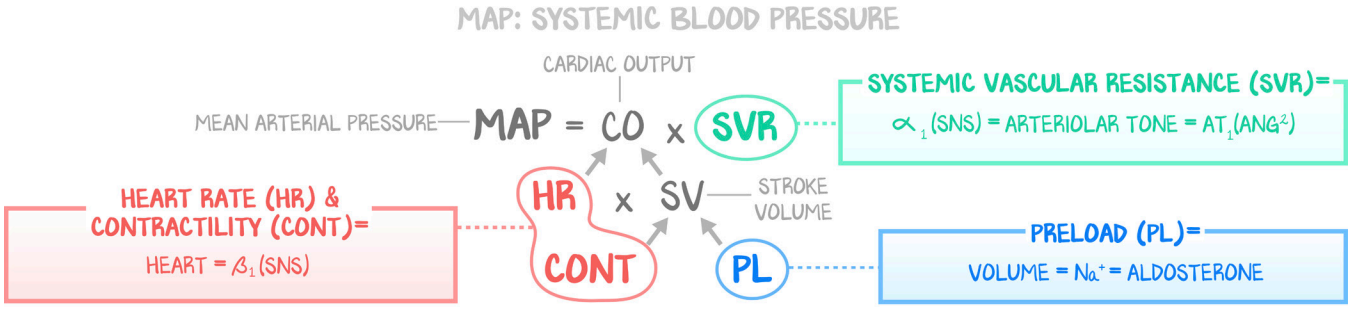

Figure 4.1: MAP Equation
This is much easier understood when Dr. Williams walks through it and points it out on the board. The MAP equation is a representation of the elements that contribute to blood pressure: contractility (CONT), preload (PL), heart rate (HR), and systemic vascular resistance (SVR). CONT and PL contribute to stroke volume (SV), and stroke volume (the amount of blood ejected with each beat) and heart rate (number of beats per minute) contribute to cardiac output (CO). If any one falls, the others must rise to compensate and prevent the MAP from falling. This compensation happens constantly, an ever-adjusting system to maintain the MAP. Get used to the colors and synonyms on the right side of the image. HR and CONT are the heart, under sympathetic nervous system control (β_1 receptors), and the heart is often a compensatory mechanism for the loss of the others. It will always be portrayed in red on the whiteboard. SVR is arteriolar tone, the degree of vasoconstriction in all arterioles combined. α1 Stimulation by the sympathetics and AT_1 receptor activation by angiotensin 2 lead to vasoconstriction and increased SVR. SVR is always portrayed in green. Finally, and the most difficult for students to accept, is preload, synonymous with volume, sodium, and the hormone aldosterone. PL is always blue.

First, we cover the mechanisms that affect MAP—the baroreceptor reflex, the renin-angiotensin-aldosterone system, and cerebral perfusion pressure—and then round out the lesson with specific additional mechanisms of regional control of vascular beds. The MAP equation is the foundation of the Cardiac module. We are going to replace MAP with myocardial work, then again with myocardial oxygen demand. Using the MAP equation to teach hypertension, myocardial work, and myocardial oxygen demand is a Dustynism. Dr. Williams used the MAP equation to train residents on the approach to shock, to low MAP in the ICU. He reappropriated it for the Basic Sciences and made it more complex in order to go beyond management and into mechanisms. And as you progress, the MAP

equation gets more complex and synonyms are added, even as complex topics are made simple. You may not like it at first (for example, *preload is aldosterone is sodium is blue*). But if you just accept that we know what we're doing and that, if you follow along, you will too, this will be a lot easier than any other way of learning it. Different areas of study, even within a domain (such as within physiology), use different words that mean the same thing. This process of educating using the MAP equation shows you how synonymous the "different" areas are.

MAP: Baroreceptors

The **baroreceptor reflex** is a neural reflex, which means it is **fast**. There is a center called the **nucleus tractus solitarius** (NTS) in the **medulla oblongata** (in the brainstem). In this lesson, NTS and medulla are used synonymously (the medulla does much more than just the NTS; you will get snippets throughout the course, but we save the discussion of the medulla for the Neuroscience module). The inputs to the NTS are neurons. The outputs of the NTS are neurons. Neurons transmit signals extremely quickly, thus the baroreceptor reflex is used to make alterations in blood pressure very quickly—in seconds (norepinephrine as a neurotransmitter) to minutes (epinephrine from the adrenal gland as a hormone). The baroreceptor reflex is also a **high-pressure sensor**. Falling blood pressure does not stimulate or inhibit the baroreceptor reflex. Rising blood pressure stimulates the baroreceptor reflex, and falling blood pressure stimulates it less. This distinction is important when comparing the next few mechanisms of global blood pressure regulation.

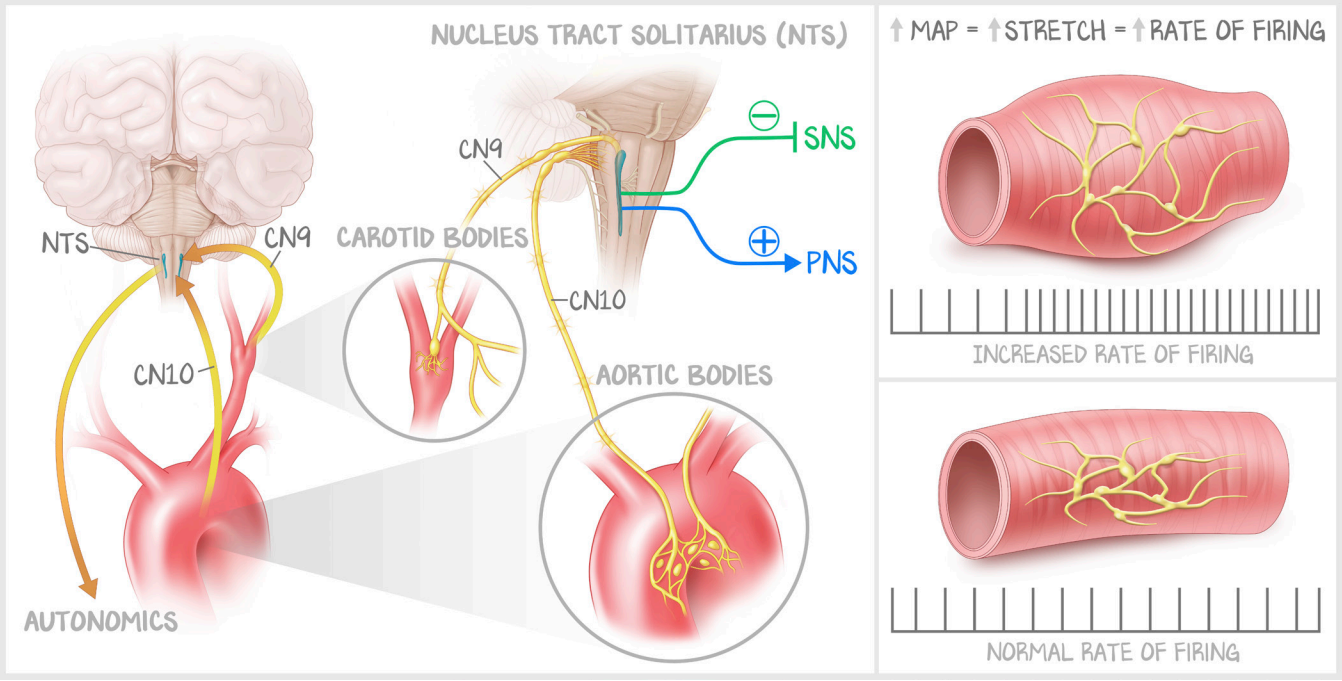

Figure 4.2: How Baroreceptors Sense Pressure
The carotid bodies and aortic bodies increase the firing rate of their neurons in response to increased stretch. Stretch is the surrogate for pressure in the baroreceptor reflex. The aortic bodies project axons to the NTS along cranial nerve X (the vagus nerve), with the carotid bodies projecting along cranial nerve IX (the glossopharyngeal nerve).

The high-pressure baroreceptors are the **carotid baroreceptors**, located at the bifurcation of the carotid arteries into the internal and external carotids, and the **aortic baroreceptors**, located on the underside of the aortic arch. The carotid bodies' nerve impulses are carried to the medulla via **cranial nerve IX** (the

glossopharyngeal nerve), whereas the aortic bodies' nerve impulses are carried to the medulla via **cranial nerve X** (the vagus nerve). The inputs into the NTS are stimulatory. When blood pressure increases, the baroreceptors are stretched. They always have some neuronal firing, even when not stretched. But as they are stretched, the frequency of their impulses increases. We're trying very hard NOT to use words you will learn in Neuroscience but have not yet learned, so if the words sound vague, they are, and it is by design.

The NTS is a nucleus (in the CNS, a nucleus is a cluster of neurons, not the DNA-containing organelle within each cell). Cells of that nucleus receive inputs from the baroreceptors. The neurons of the NTS have axonal projections to centers in the brainstem that control sympathetic and parasympathetic output. These projections are **inhibitory to the sympathetic nervous system** and **excitatory to the parasympathetic nervous system**. When the blood pressure increases, it stretches the baroreceptors; they fire more frequently into the NTS, which in turn fires more frequently, inhibiting the sympathetic nervous system and stimulating the parasympathetic nervous system.

The sympathetic nervous system (SNS; General Pharmacology #10: *Adrenergics (SNS)*) acts on effector organs through the neurotransmitter norepinephrine. Norepinephrine activates α_1 **receptors** in the peripheral vasculature, inducing the **vasoconstriction** of arterioles, and activates β_1 **receptors** on the heart, increasing both heart rate and contractility. The parasympathetic nervous system (PNS; General Pharmacology #9: *Cholinergics (PNS)*) innervates $\mathbf{M_2}$ **receptors** on the heart, slowing the heart rate down. Because the NTS inhibits the SNS and stimulates the PNS, the net effect is to **decrease arteriolar tone** (less SVR through less α_1), **decrease heart rate** (lower HR through less β_1 and more M_2), and **decrease contractility** (reduced CONT through less β_1).

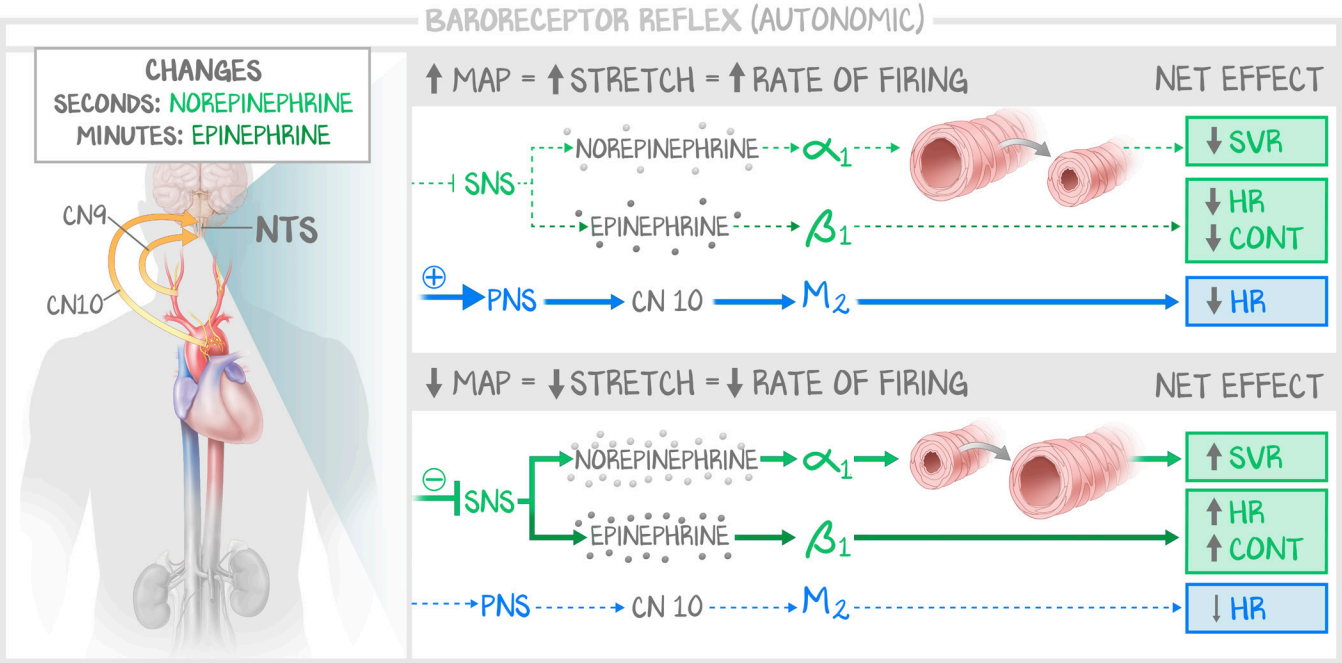

Figure 4.3: Baroreceptor Summary
Because activation of the SNS leads to the release of a peptide hormone, epinephrine, the effects of the baroreceptors are felt immediately (norepinephrine changes) and over the course of several minutes (epinephrine changes). Increased MAP leads to an increased stretch, which in turn leads to an increased rate of firing of the baroreceptors. It is being kept ambiguous (you will appreciate this joke only after Neuroscience) as to where in the medulla "the (para)sympathetics are." The overall output, however, is shown. Increased baroreceptors lead to an increase in the firing of the NTS, which in turn inhibits the SNS and stimulates the PNS, leading ultimately to decreased SVR, decreased heart rate, and decreased contractility.

Did you notice where the blood vessels that have baroreceptors lead to? The brain. The brain needs to be perfused, but not too much. The baroreceptor reflex is a safety mechanism that prevents too much blood from flowing to the brain too quickly.

MAP: RAAS

RAAS stands for the renin-angiotensin-aldosterone system. This is a high-level drive-by version of the system, which is discussed in detail in the Renal and Endocrine modules. It also is your first introduction to the Katrina switch, which is one of Dr. Williams's most cherished teaching methods (both he and learners cherish it). It explains so much pathophysiology that it comes up in most modules. Here, we want to give you a gentle introduction to this system, just enough to understand how the kidney assesses blood flow and the systemic mechanisms it uses to correct it.

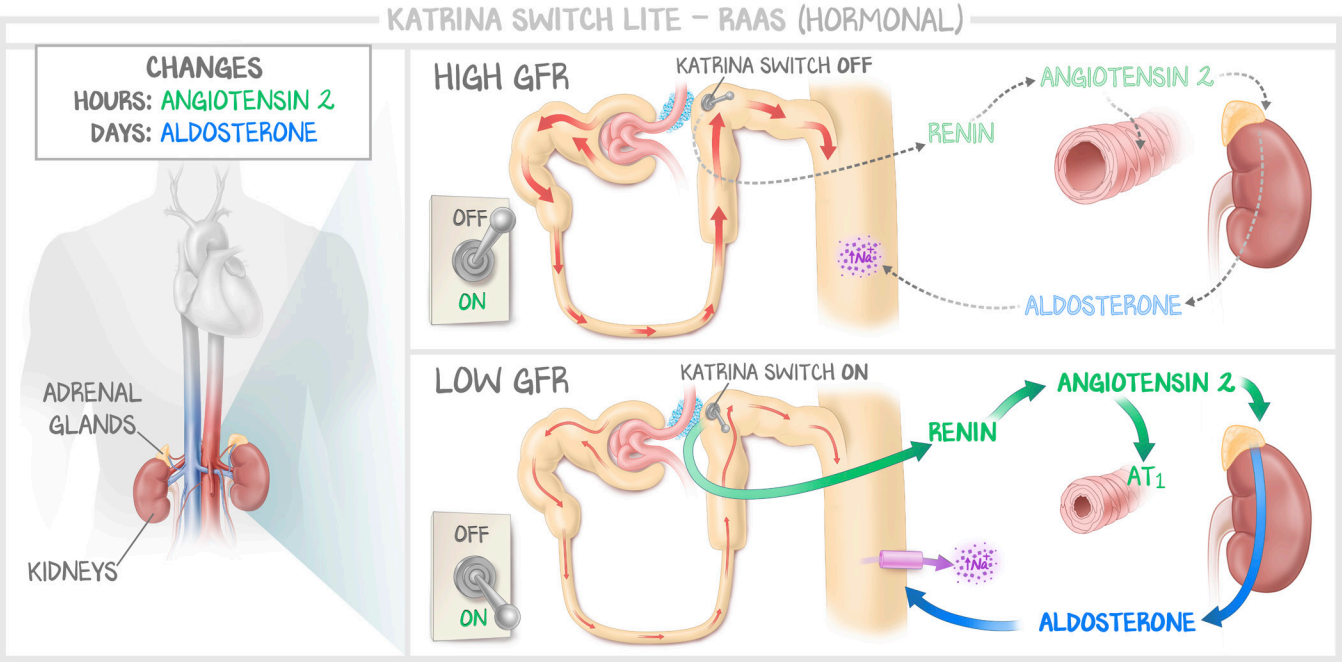

Figure 4.4: Katrina Switch Lite—RAAS
At some point in the nephron tubule that you have not yet learned (the JG apparatus of the macula densa at the start of the distal convoluted tubule), there is a flow sensor that Dr. Williams calls the Katrina switch. After he bought his first house in New Orleans, after Hurricane Katrina, not all of the construction work met the highest standards. Luckily for us, he didn't fix his light switches. Unlike most, his house had "Katrina switches," which were upside down. Down was on, up was off. If the GFR is low, the flow through the nephron will be low, too low to flip the switch up. Gravity means the weight of the switch will naturally fall to the downward "on" position. When on, the JG apparatus releases the hormone renin. Several steps, not depicted and withheld on purpose, results in the formation of angiotensin 2 (Ang 2). Angiotensin 2 activates AT_1 receptors on blood vessels, "tensing the angios," causing arteriolar vasoconstriction much like α_1 receptors do. In addition, angiotensin 2 stimulates the production of the steroid hormone aldosterone (aldo), which induces gene transcription of a sodium transporter. Sodium is reabsorbed from the nephron and put back into circulation. *Water follows salt,* and when sodium is reabsorbed, the volume comes with it.

The kidney uses the glomerular filtration rate (GFR), how much fluid is filtered at the glomerulus, to assess whether there is enough systemic perfusion pressure. The baroreceptors look for excess pressure and quiet everything down if they find it. The RAAS assesses for **too little pressure**. This has nothing to do with distension and stretch, nor does it use neural reflexes. The RAAS uses the GFR to assess the perfusion pressure and takes steps to restore it. You may feel that there is a seemingly infinite amount

you do not understand about this system. That is okay. Here's what you need this early in the organ system section of our Basic Sciences curriculum.

1. Activation of the RAAS leads to two outputs: angiotensin 2 and aldosterone.
2. Angiotensin 2 "tenses the angios," inducing vasoconstriction. Vasoconstriction increases SVR.
3. Aldosterone increases sodium reabsorption in the kidney. Water follows salt. This increases preload.
4. Activation of the RAAS is due to decreased flow through the nephron. The kidney assumes that low flow through the nephron is because of low GFR and that low GFR is because of insufficient perfusion pressure. The kidney's response, then, is to replace the circulating volume and decrease the size of the tank.

The effects of the RAAS on blood pressure occur slowly. If someone suffers an acute loss of volume—severe hemorrhage, for example—the baroreceptor reflex can increase heart rate, contractility, and systemic vascular resistance almost instantly. The RAAS cannot act fast enough to replace the lost volume. The RAAS contributes to the MAP in the short-term by increasing systemic vascular resistance through angiotensin 2. Slower than the neural responses from baroreceptor changes but also longer lasting. The RAAS contributes to long-term MAP correction by moderating **preload** through aldosterone. Aldosterone takes the longest to take effect but also lasts the longest. If someone is hemorrhaging, the endogenous systems will not be enough. That is why we administer a bolus of intravenous fluids to expand the volume and give blood to replace the lost hemoglobin.

Do not chase the details of this system. They will come. Right now, just see the RAAS as a low-perfusion sensor that uses hormones to correct the MAP (Ang 2 via SVR and aldosterone via preload). This works in conjunction with the baroreceptor reflex, a high-perfusion sensor that uses neurotransmitters to correct the MAP. Both systems play a role when the pressure is too high and when it is too low. And although we have not shown you how, they are also intimately interrelated. That is a discussion for future lessons.

MAP: Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) is a specialized override of the system. The brain is encased within the skull, floating in a small amount of cerebrospinal fluid. There isn't a whole lot of room in the skull. So if there is ever something that isn't supposed to be there—cancer, bleed, infection—something that takes up space, there may be an increased intracranial pressure. Arteries distend and recoil, and blood flows through the artery. In the normal state, there is always enough perfusion pressure for blood to flow through the artery, and the artery is always kept open. But if there were a competing force, one external to the artery that collapses it, the MAP would be used first to keep the vessel open, then what is left over to push the blood through the arteries. The **cerebral perfusion pressure** is whatever is left over. The pressure that is both the distending force and the perfusing pressure is the **MAP**. The pressure that is opposing the distending force, collapsing the vessel, is the **intracerebral pressure (ICP)**. Said mathematically,

$$CPP = MAP - ICP$$

If the cerebral perfusion pressure falls, it is either because the MAP is falling or because the ICP is rising. The "brain" (vague on purpose) has a center that monitors CPP. If CPP falls, it sends out an override signal to increase MAP, restoring CPP. It does that with a **sympathetic discharge**, leading to increased heart rate, increased contractility, and increased vasoconstriction. But the cerebral vasculature has very few α_1 adrenergic receptors, so the cerebral arteries don't feel the sympathetic discharge, they just feel the increased flow provided by an increased systemic MAP.

This mechanism is great if the initial insult is a fall in the MAP—the brain picks up the slack for the baroreceptors. A sympathetic discharge will improve the MAP by clamping down on the vasculature, increasing the heart rate, and increasing the contractility of the heart, restoring cerebral perfusion pressure. After all, chances are if the MAP is low for the brain, the MAP is low everywhere. But now go the other way. Something other than the brain (edema, a bleed, cancer, whatever) is increasing the ICP. The CPP falls, and the brain tells the cardiovascular system to increase the MAP. Only, the MAP is already normal, and increasing the MAP does improve the CPP, but also blows out every other organ.

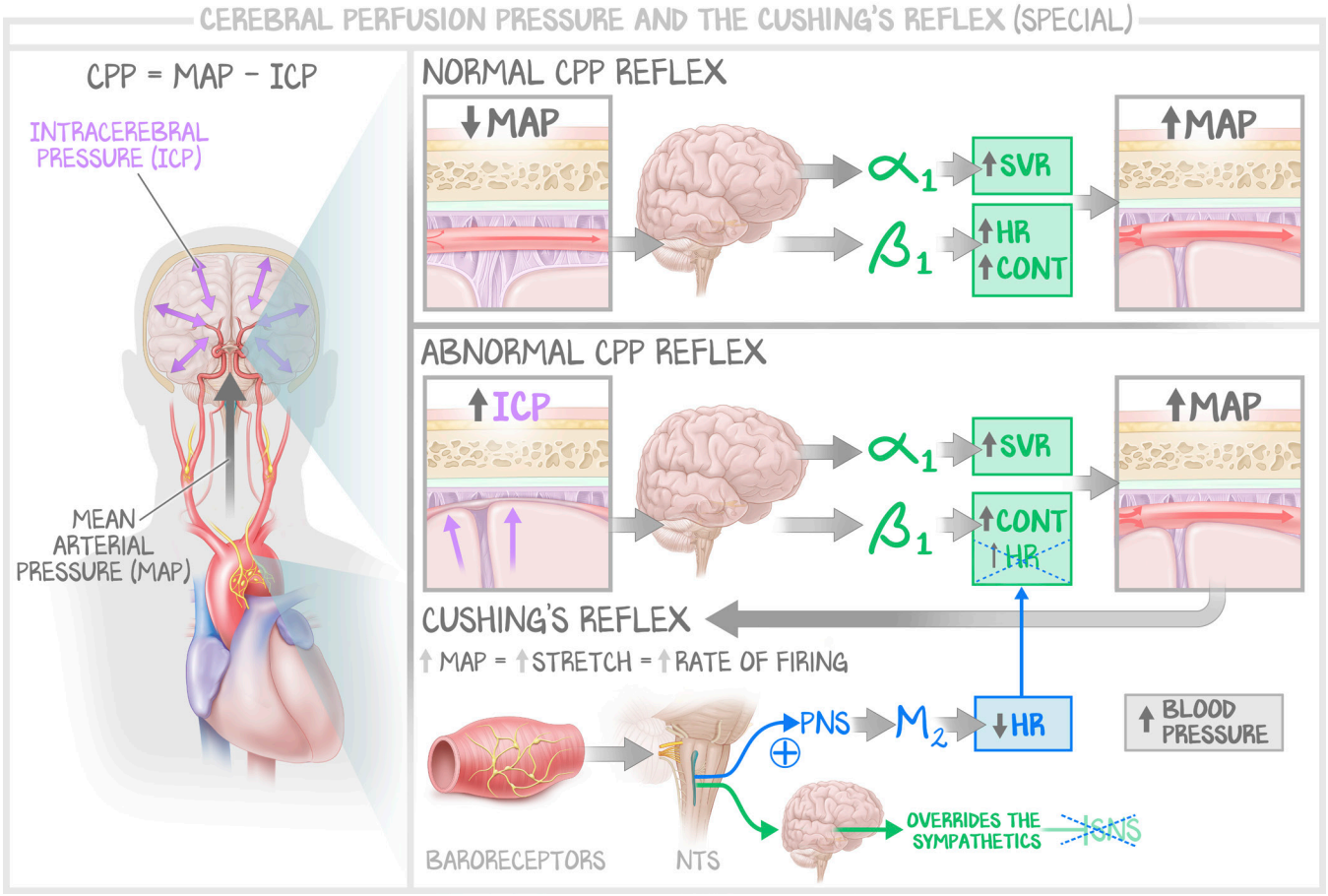

Figure 4.5: Cerebral Perfusion Pressure and the Cushing Reflex
If the MAP falls, resulting in a decreased CPP, the CPP reflex corrects the MAP and restores both the systemic perfusion and cerebral perfusion (normal CPP reflex). If the insult is increased ICP, the CPP reflex is still employed to restore the CPP. But in this instance, the rest of the body must endure a very elevated MAP, which could compromise tissues just as much as low pressure does. Because the baroreceptors are assessing MAP, and MAP is high, they send their signals to the NTS, which activates the parasympathetic nervous system and inhibits the sympathetic nervous system. The CPP reflex stimulates only the sympathetic nervous system. Thus, SVR and contractility increase, while ultimately, heart rate decreases. This is called Cushing's reflex and, if found, intracranial pathologies should be pursued.

Regional Vascular Beds: Autoregulation

The tissues perfused by the capillaries of an arteriole inform the arteriole of what perfusion pressure they want via metabolites and local paracrine signals. The arterioles then maintain that perfusion pressure, smooth out any variation due to systole and diastole, and protect against any swings in MAP. This is what is meant by autoregulation.

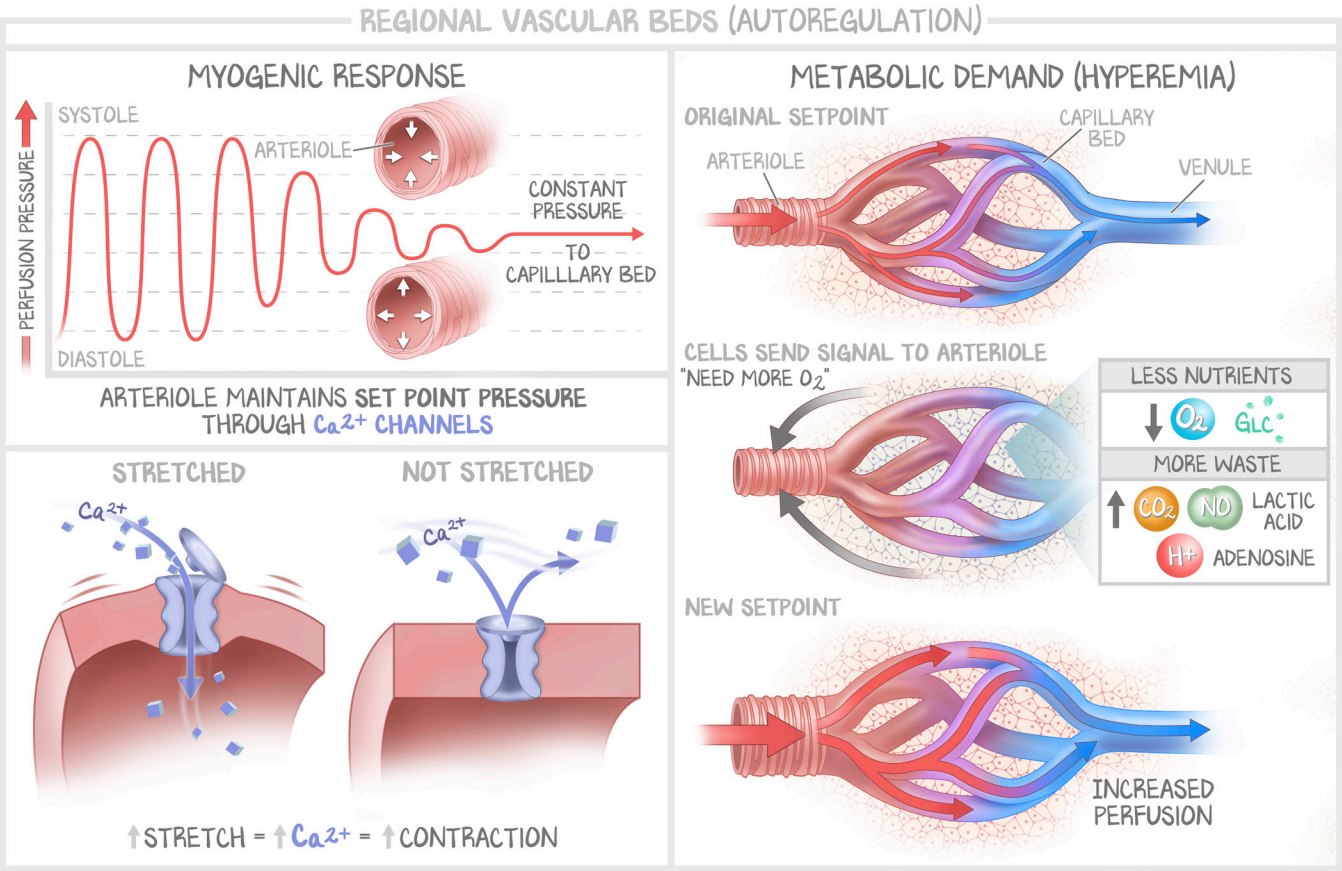

Figure 4.6: Autoregulation
At left, the myogenic response keeps the arteriolar tone to ensure that the capillaries receive the perfusion pressure the tissues ask for and eliminate the variations in systole and diastole. The arterioles maintain this pressure through the regulation of stretch-gated calcium channels. At right, metabolic demand (hyperemia) informs the arteriole of how much pressure is needed.

The cells of the tissue **inform the arteriole** using a phenomenon called **hyperemia**, better termed (by us) **metabolic demand**. What it comes down to is how active the tissues are. If they are very active, they need more oxygen and glucose, so they will need more blood flow. If they aren't very active, they don't need more oxygen and glucose, so they will need less flow. Blood follows the path of least resistance, and resistance is controlled by the radius of the arteriole. The **absence of nutrients** (low tissue oxygen and glucose) and the **presence of waste products** (high carbon dioxide, hydrogen ions, low pH, and high lactic acid) inform the arteriole that more flow is needed and to **vasodilate**. In every vascular bed (except the kidneys), **nitric oxide** and **adenosine** induce vasodilation. The tissues' metabolic activity informs the arteriole what those capillaries' perfusion pressure should be. Vasodilation to let more flow in, vasoconstriction if less is needed.

The arteriole **maintains the perfusion pressure** using a phenomenon called the **myogenic response**. In the CPP section, we talked about how the MAP distends the artery to keep it open and how what is left over is the perfusion pressure, driving blood forward. Something similar happens here, only at the microscopic arteriolar level. *When stretched, the VSMCs contract back.* Systole peaks at a high pressure, which, like the ventricle does to the aorta, would provide both a forward pressure down the arterial tree and a distending force into the walls of the arteriole. However, that distending force does not distend the arteriole. The increased perfusion pressure stretches the VSMCs of the tunica media, opening stretch-activated calcium channels. The influx of calcium enables increased tone. During diastole, there is the lowest perfusion pressure and no distending force, so the stretch-gated calcium channels close. This is true across a wide variety of MAPs. The myogenic response is the phenomenon wherein the arteriole tolerates variations both in systolic and diastolic pressures on a second-to-second basis (ensuring that there is little to no variation after the arterioles and the capillaries see a constant perfusion pressure) AND a variety of MAPs.

The **pulmonary arterioles work differently**. Pulmonary arteries do not bring oxygenated blood to the lungs; systemic arteries, branches of the aorta, bring oxygenated blood to the pulmonary tissues. The pulmonary arteries are designed to bring deoxygenated blood to the pulmonary alveoli in order to expel carbon dioxide and get oxygen from the alveoli. Because the purpose of the pulmonary arteries is to grab oxygen from the alveoli, the pulmonary vasculature maximizes blood flow into the alveoli with the most oxygen and minimizes blood flow to the regions with the least oxygen. **Tissue hypoxemia** in the alveoli of the lung **induces vasoconstriction**. The mechanism is not elucidated. We discuss this further in the Pulmonology module.